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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	17

DATE MAILED: 09/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/843,250	PARALES ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 30-38* is/are pending in the application.

4a) Of the above claim(s) *38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 30-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-13 and 30-38 are pending.

Applicant's amendment of claims 1-13 and 30-37, and amendments to the specification in Paper No. 16, filed on 6/25/2003 are acknowledged.

As indicated in previous Office Action Paper No. 15, mailed on 3/7/2003, claim 38 was withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an non-elected invention with traverse in Paper No. 14, filed on 12/27/2002. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Modified naphthalene dioxygenases and methods of use", or similar. Appropriate correction is required.

Drawings

2. The drawings submitted on 6/25/2003 have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-13 and 30-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claims 1, 4, and 7 (claims 2-3, 5-6, 8-13 and 30-37 dependent thereon) are indefinite in the recitation of "substituted amino acid at the position corresponding to position 352, and a substituted amino acid at the position corresponding to position 201, 202, 260, 316, 351, 358, 362, or 366 of SEQ ID NO: 26" for the following reasons. While it is clear that positions 201, 202, 260, 316, 351, 358, 362, or 366 refer to SEQ ID NO: 6, there is no sequence identifier associated with position 352. Therefore, in the absence of a sequence identifier, one cannot determine which position is being referred to. If the intended sequence identifier for position 352 is SEQ ID NO: 26, it is suggested that the term be replaced with "substituted amino acid at the position corresponding to position 352 of SEQ ID NO: 26, and a substituted amino acid at the position corresponding to position 201, 202, 260, 316, 351, 358, 362, or 366 of SEQ ID NO: 26", or similar. For examination purposes, the suggested language will be used. Correction is required.

6. Claim 2 (claims 8-10 dependent thereon) is indefinite in the recitation of "complex of claim 1 having an alpha-subunit that comprises an amino acid other than phenylalanine at position 352 of SEQ ID NO: 26" for the following reasons. As written, it is unclear if the claim is limited to a complex having an alpha-subunit wherein said subunit comprises SEQ ID NO: 26

with a substituted amino acid at position 352 of SEQ ID NO: 26, or if the claim is directed to the complex of claim 1 wherein the alpha-subunit can comprise any sequence, and wherein said alpha-subunit comprises an amino acid other than phenylalanine at a position corresponding to position 352 of SEQ ID NO: 26. For examination purposes, it will be assumed that the claim is limited to a complex having an alpha subunit wherein said subunit comprises SEQ ID NO: 26 except that the phenylalanine residue at position 352 of SEQ ID NO: 6 has been substituted with different amino acid. Correction is required.

7. Claim 3 (claims 30-37 dependent thereon) is indefinite in the recitation of "complex of claim 1 having an alpha subunit that comprises a substituted amino acid at position 201, 202, 260, 316, 351, 352, 358, 362 or 366 of SEQ ID NO: 26" for the following reasons. As written, it is unclear if the claim is further limiting to a complex having an alpha subunit that comprises SEQ ID NO: 26 with amino acid substitutions at positions 201, 202, 260, 316, 351, 352, 358, 362 or 366 of SEQ ID NO: 26, or if the claim is directed to a complex having an alpha subunit comprising any sequence, and wherein said alpha subunit comprises different amino acids at positions corresponding to positions 201, 202, 260, 316, 351, 352, 358, 362 or 366 of SEQ ID NO: 26. For examination purposes, it will be assumed that the claim is directed to a complex comprising an alpha subunit, wherein said subunit comprises SEQ ID NO: 26 with amino acid substitutions at positions 201, 202, 260, 316, 351, 352, 358, 362 or 366 of SEQ ID NO: 26. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 4-7, 11-13 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. This rejection, which has been discussed at length in Paper No. 15, mailed on 3/7/2003, was applied to claims 1-8, 11-12, 30-37 and is now applied to amended claims 1, 4, 11-13 for the reasons of record.

11. Applicants argue that many alpha subunits of naphthalene dioxygenases which correspond to SEQ ID NO: 26 are known in the art and that the specification teaches examples of such dioxygenases as well as examples of representative amino acid substitutions corresponding to position 352 in SEQ ID NO: 26. Furthermore, Applicants argue that the specification discloses methods to determine if a naphthalene dioxygenase complex or naphthalene dioxygenase related complex catalyzes the oxidations of an aromatic substrate in Examples 4, 6, and 7. Applicants submit that the claims are now amended to include a structure and function which can be used to determine the scope of the claims.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The term "naphthalene dioxygenase related complex" is no longer considered indefinite and has been interpreted as "any dioxygenase complex which can catalyze the oxidation of an aromatic substrate" in view of the recitation in claim 1 of "wherein the

complex or the related complex catalyzes oxidation of an aromatic substrate". As such, the claims as amended are now directed to any dioxygenase complex which can catalyze the oxidation of an aromatic substrate wherein said complex can comprise any alpha subunit, and wherein said subunit comprises amino acid substitutions at positions corresponding to specific positions within SEQ ID NO: 26. While the Examiner acknowledges the teachings of the specification in regard to other naphthalene dioxygenases known in the art , which amino acids in those dioxygenases correspond to those being substituted in SEQ ID NO: 26, and tests to determine enzymatic activity, the Examiner disagrees with Applicant's contention that the claimed invention is adequately described. As indicated in previous Office Action Paper No. 15, the specification is silent in regard to (1) the critical structural elements required in any polypeptide complex to obtain any NDO or any dioxygenase capable of catalyzing the oxidation of any aromatic compound, (2) how to determine which amino acids in any alpha subunit of any NDO or any dioxygenase capable of catalyzing the oxidation of any aromatic compound correspond to those of SEQ ID NO: 26, as recited in the claims, or (3) which aromatic compounds would be oxidized by the genus of polypeptide complexes claimed. While it is agreed that the specification discloses other NDOs and those amino acids which are expected to correspond to those specific positions within SEQ ID NO: 26 recited in the claims, the specification does not disclose which aromatic compounds will be oxidized by other NDOs comprising the amino acid substitutions recited nor does it disclose which amino acids can be placed in those positions to obtain a polypeptide complex capable of catalyzing the oxidation of a specific aromatic compound. As indicated previously, while the argument can be made that the claimed NDO and dioxygenase complexes are adequately described since other functional

homologs can be isolated by structural similarity, the state of the art teaches the unpredictability of assigning function based on structural homology. The genus of polypeptides complexes claimed is a genus with the potentiality of encompassing an extremely large number of different species due to the extremely large number of aromatic compounds which can be oxidized by those complexes. It is not expected that one NDO or dioxygenase complex can catalyze the oxidation of any aromatic compound. Therefore in view of the substantial variation within the genus claimed, one cannot reasonably conclude that the few species disclosed is sufficient to adequately described the claimed invention.

13. Claims 1, 4, 11-13 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the Pseudomonas NDO which corresponds to Swiss Prot accession number P23094 wherein (1) the phenylalanine residue at position 352 of the alpha subunit (SEQ ID NO: 26) has been substituted with valine, glycine, alanine, threonine, leucine or isoleucine, or (2) the residues at positions 201, 202, 260, 316, 351, 358, 362, or 366 in the alpha subunit (SEQ ID NO: 26) have been substituted, does not reasonably provide enablement for any dioxygenase complex capable of catalyzing the oxidation of any aromatic compound wherein the alpha subunit of said dioxygenase complex comprises amino acid substitutions at positions which correspond to specific positions within SEQ ID NO: 26 as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

14. This rejection, which has been discussed at length in Paper No. 15, mailed on 3/7/2003, was applied to claims 1-8, 11-12, 30-37 and is now applied to amended claims 1, 4, 11-13 for the reasons of record.

15. Applicants argue that the claims have been amended to include a sequence identifier to which the amino acid position of specific amino acid substitutions can be referenced. Applicants also submit that the claims are now directed to a naphthalene dioxygenase complex or a related complex that catalyzes oxidation of an aromatic substrate. Applicants argue that one of skill in the art would be able to identify corresponding amino acids to the specific positions described for SEQ ID NO: 26, and determine if the claimed protein complexes comprising the modified alpha subunit can catalyze the oxidation of an aromatic substrate according to the directions provided in the specification without undue experimentation.

16. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. As indicated above, the claims as amended now encompass any dioxygenase complex which can catalyze the oxidation of an aromatic substrate wherein said complex can comprise any alpha subunit, and wherein said subunit comprises amino acid substitutions at positions corresponding to specific positions within SEQ ID NO: 26. While the Examiner acknowledges the teachings of the specification in regard to other naphthalene dioxygenases known in the art , which amino acids in those dioxygenases disclosed correspond to those being substituted in SEQ ID NO: 26, and tests to determine enzymatic activity, the Examiner disagrees with Applicant's contention that the claimed invention is enabled for the full scope of the claims. It is reiterated that the specification is silent in regard to (1) the critical structural elements required in any polypeptide complex to obtain any NDO or any dioxygenase

capable of catalyzing the oxidation of any aromatic compound, (2) how to determine which amino acids in any alpha subunit of any NDO or any dioxygenase capable of catalyzing the oxidation of any aromatic compound correspond to those of SEQ ID NO: 26, as recited in the claims, (3) which aromatic compounds would be oxidized by the genus of polypeptide complexes claimed, or (4) any correlation between the amino acids which can be placed instead of those found in the wild-type subunit at the recited positions and the identity of the aromatic compound which can be oxidized. As indicated previously, while the argument can be made that the claimed invention is enabled since other functional homologs can be isolated by structural similarity, the state of the art teaches the unpredictability of assigning function based on structural homology. Therefore, in the absence of additional guidance as to how structure correlates with function, it is unclear as to how one of skill in the art can reasonably conclude that the disclosure of a few examples is sufficient to enable the skilled artisan to (1) isolate any NDO or dioxygenase capable of catalyzing the oxidation of any aromatic compound, (2) determine the corresponding amino acids in any alpha subunit of any NDO or any dioxygenase as claimed to the specific amino acid positions in SEQ ID NO: 26 recited, and (3) determine which aromatic compounds can be oxidized by all the protein complexes encompassed by the claims. Thus, in view of what is disclosed by the specification, the teachings of the prior art, and the unpredictability of the art in regard to assigning function based on structural homology, one of skill in the art would have to go through the burden of undue experimentation to enable the full scope of the claims.

Claim Rejections - 35 USC § 102

17. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

18. Claims 1-8, 11-12, 30-37 were rejected under 35 U.S.C. 102(b) as being anticipated by Jiang et al. (J. Bacteriol. 178(11):3133-3139, 1996). This rejection has been discussed at length in Paper No. 15, mailed on 3/7/2003.

19. Applicants argue that the claims are now directed to naphthalene dioxygenases that include an alpha subunit that has or corresponds to SEQ ID NO: 26 and that Jiang et al. does not teach a naphthalene dioxygenase as that recited in the claims. Applicant's arguments have been fully considered. In view of Applicant's amendment of claims 1-8, 11-12 and 30-37, which are now directed to (1) a naphthalene dioxygenase complex or any dioxygenase complex comprising the polypeptide of SEQ ID NO: 26 with amino acid substitutions at specific locations within SEQ ID NO: 26, or (2) a naphthalene dioxygenase complex or any dioxygenase complex comprising an alpha subunit with specific amino acid substitutions at positions corresponding to positions within SEQ ID NO: 26, this rejection is hereby withdrawn.

20. Claims 1-8, 11-12, 30-37 were rejected under 35 U.S.C. 102(b) as being anticipated by Mondello et al. (Applied and Environmental Microbiology 63(8):3096-3103, August 1997). This rejection has been discussed at length in Paper No. 15, mailed on 3/7/2003.

21. Applicants argue that the claims are now directed to naphthalene dioxygenases that include an alpha subunit that has or corresponds to SEQ ID NO: 26 and that Mondello et al. does not teach a naphthalene dioxygenase as that recited in the claims. Applicant's arguments

have been fully considered. In view of Applicant's amendment of claims 1-8, 11-12 and 30-37, which are now directed to (1) a naphthalene dioxygenase complex or any dioxygenase complex comprising the polypeptide of SEQ ID NO: 26 with amino acid substitutions at specific locations within SEQ ID NO: 26, or (2) a naphthalene dioxygenase complex or any dioxygenase complex comprising an alpha subunit with specific amino acid substitutions at positions corresponding to positions within SEQ ID NO: 26, this rejection is hereby withdrawn.

Conclusion

22. No claim is in condition for allowance.

23. Applicant's amendment of claims 1-13 and 30-37 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

25. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
September 5, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1900~~ 1600